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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/543,679	04/04/2000	Jonathan W. Nyce	EPI-067191	6742

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EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 02/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/543,679	NYCE ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *92-125* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *92-125* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4-04-2000*. + 2-27-02
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

1. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 or 119(e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number. In the instant case, Applicants claim benefit to provisional applications 60/095,212 and 60/127,958, in addition Applicants claim priority to applications 08/474,497, 08/472,527, and 09/093,972 however there is no reference to these Applications in the first line of the specification as filed.

Specification

2. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 250 words. It is important that the abstract not exceed 250 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

Response to Amendment

3. The Declaration under 37 CFR 1.132 filed 11-24-03 is insufficient to overcome the rejection of claims 92-125 based upon 35 USC 112 1st paragraph as set forth in the present Office action because: The *in vivo* data provided in the Declaration filed 11-24-03 comprises the administration of antisense oligonucleotides that were not part of the specification as originally filed. For example, oligonucleotide EPI-4067 was not disclosed in the specification as filed, the specification as filed disclosed oligonucleotides EPI 1857 and EPI-2945 as inhibitors of IL-5 and IL-4 respectively. Therefore, the ordinary skilled artisan using the specification as filed a guideline, would not have been able to produce the results obtained in the Declaration without first undertaking trial and error experimentation in order identify the particular antisense oligonucleotides used in the experiments described in the Declaration. In the instant case, the contents of the Declaration filed 11-24-03 is not commensurate with the scope of the claimed invention, since the experiments set forth in the Declaration comprise the use of compounds that were not previously described in the specification as originally filed.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 99-100, 104, 107, 117, and 124 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 99 recites the limitation "wherein the pharmaceutical composition is administered by inhalation directly to the airway or lung of the subject." This limitation is vague and indefinite since it is apparent that the pharmaceutical composition of claim 92 is administered to that airways of a subject (see line 2 of claim 92), and it is immediately apparent that the lungs of subject is directly linked to the airway of a subject, therefore it is unclear how administration is to be achieved via the airway or the lung of a subject.

7. Claims 100 and 117 recite wherein the antisense oligonucleotide is "antisense to the initiation codon, the coding region or the 5' or 3'intron-exon junction of a target polypeptide.." This phrase is vague and indefinite since it appears that the antisense oligonucleotides of the present invention are "antisense" to a target polypeptide. One of ordinary skill in the art would immediately recognize that the term "antisense" refers to sequences that are complementary to the mRNA sequence encoded by a target gene, and further that the initiation codon, the coding region, and the 5' and 3' intron-exon junctions referred to in this claim refer to an mRNA sequence and not to a polypeptide sequence.

8. Claim 104 (line 3) recites the limitation "or lung inflammation," however there is lack of sufficient antecedent basis for this limitation in claim 92. Claim 121 (line 4) recites the

limitation " or lung inflammation," there is lack of sufficient antecedent basis for this limitation in claim 109.

9. Claims 107 and 124 recite, "wherein the antisense oligonucleotide is antisense to the initiation codon, the coding region or the 5' or 3' intron-exon junctions of a gene encoding bradykinin B2 receptor." This phrase is vague and indefinite since it appears that the oligonucleotides of the present invention are "antisense" to a target gene. One of ordinary skill in the art would immediately recognize that the term "antisense" refers to sequences that are complementary to the mRNA sequence encoded by a target gene, and further that the initiation codon, the coding region, and the 5' and 3' intron-exon junctions referred to in this claim refer to an mRNA sequence and not to a gene sequence.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 92-125 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims read on a method of delivering a pharmaceutical composition to a target polynucleotide comprising administering at least one antisense oligonucleotide effective alleviate hyper-responsiveness to adenosine or increased levels of adenosine, or to alleviate bronchoconstriction, asthma, or lung allergy, wherein the oligonucleotide is 7 to 60 nucleotide

long and comprises 15% or less adenosine. This method reads on target polynucleotides that are beyond the scope of the contents of the specification as filed. First it is noted that there is no direct relationship between the "target polynucleotide" (line 2) recited in claim 92, and the "antisense oligonucleotide" (see line 4) recited in claim 92. The antisense oligonucleotides of claim 92 are described by function, specifically that the antisense oligonucleotide is effective alleviate hyper-responsiveness to adenosine or increased levels of adenosine, or to alleviate bronchoconstriction, asthma, or lung allergy. However, there is no clear structural description of the antisense oligonucleotide in relationship to its ability to be effective to alleviate hyper-responsiveness to adenosine or increased levels of adenosine, or to alleviate bronchoconstriction, asthma, or lung allergy. Although claim 92 recites wherein the antisense oligonucleotide is 7 to 60 nucleotides long and comprises 15% or less adenosine, this structural information is not sufficient to provide an oligonucleotide that functions to alleviate conditions associated with increased levels of adenosine, for example an asthmatic condition. According to Krieg et al., and oligonucleotide comprising 15 % adenosine (TCCATGACGTTCCTGACGTT) was not able to prevent the development of an inflammatory condition associated with a murine model of asthma. However, oligonucleotides comprising 15% adenosine, the identical sequence, TCCATGACGTTCCTGACGTT, and an unmethylated CpG motif at the underlined positions of this sequence was able to prevent the development of an inflammatory cellular infiltrate and eosinophilia in a murine model of asthma (see US Patent No. 6,207,646 B1, col. 34, lines 28-45). Therefore, the limitations describing the percent adenosine in the antisense oligonucleotide and its length are insufficient to design an effective antisense oligonucleotide that is capable to to alleviate bronchoconstriction, asthma, or lung allergy. It is clear that knowledge of the target

polynucleotide to which the oligonucleotide is to be "antisense," is required in order to design an effective antisense oligonucleotide.

Moreover, it is clear that the potential number of target polynucleotides that may be used to design antisense oligonucleotides that may potentially function to alleviate broncho-constriction, asthma, or lung allergy, is unknown and further may include numerous structural variants. Furthermore, the genus of target polynucleotides and antisense oligonucleotides are highly variant because a significant number of structural differences between the genus members are permitted, and neither the specification or the claims provide any guidance as to what specific changes should be made. Furthermore, there are no common structural attributes shared among the members of the claimed genus of nucleic acid molecules that would allow one of skill in the art to clearly distinguish all the members of the claimed genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is required. Since the disclosure fails to describe the common attributes or characteristics that identify the members of the claimed genus, and because the genus is highly variant, the disclosed sequences alone are not sufficient to describe the claimed genus. Additionally, it is clear that potential antisense oligonucleotides must also be tested in order to determine if they are effective to alleviate bronchoconstriction, asthma, or lung allergy. Therefore, further experimentation is required in order to identify the full scope of compounds that are encompassed by the claimed genus of antisense oligonucleotides and target polynucleotides that are encompassed by the instant claims. Thus, applicant was not in possession of the claimed genus.

12. Claims 92-125 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using pharmaceutical compositions comprising antisense oligonucleotides targeting adenosine receptor mRNA effective in treating an asthmatic condition provoked by the administration of adenosine, does not reasonably provide enablement for the treatment of hyper-responsiveness to adenosine or increased levels of adenosine, or to alleviate bronchoconstriction, asthma, or lung allergy by the administration of antisense oligonucleotides targeting any other mRNA target. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 92-125 read on an in vivo method of delivering a pharmaceutical composition to a target polynucleotide, comprising administering to the airways of a subject a pharmaceutical composition of respirable or inhalable particle size of 0.5 mm to 10 mm in size or 10mm to 500 mm in size comprising at least one antisense oligonucleotide effective to alleviate hyper-responsiveness to adenosine, or increased levels of adenosine, bronchoconstriction, asthma, or lung allergies.

The specification as discloses only antisense oligonucleotides targeting mRNAs encoding adenosine receptors. There are no guidelines or instruction to teach one of skill in the art to make and or use a pharmaceutical composition, comprising an antisense targeting any and all genes, to alleviate the diseases recited in the instant invention. The specification discloses only one functional antisense targeting adenosine receptors in aerosolized form that are effective in alleviating bronchoconstriction, allergies and inflammation.

The specification fails to provide an enabling disclosure for how to treat bronchoconstriction, inflammation, allergies, and the multiple forms of cancer recited in the instant invention by the administration of a pharmaceutical composition comprising an antisense oligonucleotide targeting any gene. In the absence of a comprehensive understanding of the role of a particular gene product in the etiology of a given disease state, it is impossible to predict if the inhibition of that gene product would yield any useful or efficacious results. Furthermore, even if the role of a given gene product is well understood, due to the unpredictability regarding the behavior of antisense based therapeutics that one cannot predict whether an oligonucleotide targeted to the gene in question would effectively reduce its expression in *vivo*. The design of antisense oligonucleotides to a target polynucleotide, as stated above, the instant claims read on antisense oligonucleotides effective to alleviate hyper-responsiveness to adenosine, or increased levels of adenosine, or to alleviate bronchoconstriction, asthma, or lung allergy, wherein said oligonucleotides are antisense to target polynucleotides of unknown structure, including all polymorphic and allelic variants of said target polynucleotide. Crooke (1999; pages 3-5) describes a variety of factors that influences the activity of antisense-based compounds that must be considered when designing an antisense oligonucleotide. Crooke teaches that variations in cellular uptake and distribution of antisense oligonucleotides are influenced by a variety of factors such as: length of the oligonucleotide, modifications to the oligonucleotide structure, the nucleotide sequence of the oligonucleotide and the type of cell the antisense is administered to. Furthermore, Crooke describes the influence of non-antisense effects, for example, phosphorothioate oligonucleotides tend to bind to many proteins, this protein binding may influence cell uptake, distribution, metabolism and excretion of the oligonucleotide. Such

protein binding may produce effects that can be mistakenly interpreted as antisense activity, and such binding may also inhibit antisense activity of some oligonucleotides. In addition to proteins, oligonucleotides may interact with other biological molecules, such as lipids, or carbohydrates, and such interactions, like those with proteins, will be influenced by the chemical class of oligonucleotide studied (Crooke, 1999; p. 5). Crooke clearly teaches that there is a significant level of factors which influence the behavior of antisense based compounds thereby rendering the activity of antisense compounds unpredictable.

The specification as filed does not enable anyone of skill in the art to practice the instant invention throughout the full scope of the claimed invention. This conclusion is based upon the known unpredictability in the art regarding antisense based therapeutics, the lack of guidance, direction or description provided by the specification, the limited number of working examples provided by the specification, the breadth of the claims, and the amount of experimentation need to practice the invention.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 92-106, 108-123 and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al. in view of Jacobson et al., Debs et al. and Burns et al.

Krieg et al. discloses nucleic acid molecules that can be administered to treat or prevent the symptoms of asthma (see col. 6, lines 59-61). In one embodiment, Krieg et al. discloses the

nucleic acid molecule TCCATGACGTTCCTGACGTT (20 nucleotides in length), comprising an unmethylated CpG motif at the underlined positions (col. 34, lines 27-45). It is noted that this oligonucleotide comprises 15% adenosine residues. This oligonucleotide was used to prevent the development of an inflammatory cellular infiltrate and eosinophilia in a murine model of asthma. Krieg et al. disclose other forms of immunostimulatory nucleic acid, for example TCCATGTCGGTCCTGATGCT (20 nucleotides in length, see Table 1, SEQ ID NO: 31), this nucleic acid comprises 10% adenosine. The immunostimulatory nucleic acid molecules of Krieg et al. may be administered alone or in a formulation as a delivery complex to a subject. A preferred route of administration includes oral administration (col. 34, lines 46-51). The oligonucleotides of Krieg et al. are preferably resistant to degradation, and may comprise modifications to stabilize the oligonucleotide against degradation. For example, Krieg et al. teach that the nucleic acids of the invention may comprise at least a partial phosphorothioate modified backbone. Additionally, the nucleic acids may comprise 2'-O-methyl modifications (see col. 32). It is noted that the instant claims are directed to the administration of antisense oligonucleotides, although Krieg et al. does not explicitly state that the oligonucleotide according to TCCATGACGTTCCTGACGTT is an antisense oligonucleotide, absent evidence to the contrary this sequence is an antisense oligonucleotide. For example, this sequence is "antisense" to (i.e. reverse complement of) mouse endogenous murine leukemia mink cell focus-forming (MCF) pol protein (3' end), and envelope protein (5' end) mRNAs, clone T-7.2. (Genbank Acc. No. M19049.1) at nucleotides 243-261.

However, Krieg et al. does not teach the use of oligonucleotides comprising 5% or less adenosine for the treatment of conditions associated with increased levels of adenosine,

including bronchoconstriction, asthma, or lung allergy. Additionally, Krieg et al. does not teach the delivery of antisense in a pharmaceutical composition of a respirable or inhalable particle size of 0.5μm to 10 μm or 10μm to 500μm in size.

Jacobson et al. teach that increased levels of adenosine in asthmatics result in bronchoconstriction (col. 1, lines 43-44). High concentrations of adenosine in airway fluids results in the activation of A3 receptors present on eosinophils. This accumulation of activated eosinophils results in the exacerbation of the inflammatory and allergic responses (col. 6, lines 58-67). Moreover, Jacobson et al. teach that eosinophil activation is a component of: myocardial reperfusion injury, hypersensitivity reactions (asthma, allergic rhinitis, and urticaria), ischemic bowel disease, autoimmune inflammation, and atopic dermatitis and many other diseases. The Jacobson et al. invention consists of the use of any of a series of highly specific A3 adenosine receptor antagonists to treat or prevent these diseases and pathologic effects that result from eosinophil activation (see example 16).

Debs et al. teach the delivery of nucleic acid compounds to the airways of a patient by means of a nebulizer that produces sufficiently small particles, for example particles of less than 5.0 μm, or more preferably 0.2 to about 4.0 μm. As an alternative to selecting small mean particle diameters to achieve substantial distal airway and alveolar deposition, a very high dosage of the lipid-carrier nucleic acid can be administered with a larger mean particle diameter. A proviso to such an approach is that the particular lipid carrier nucleic acid complex is chosen that is not too irritating at the required dosage and that there be a sufficient diameter in the 0.5 to about 5μm range to allow for deposition in the aveoli. Suitable mean particle diameter will be most preferably from about 5 μm to about 10 μm (see page 31, lines 4-19). Debs et al. teach that

nebulizers useful for airway delivery include those typically used in the treatment of asthma (see page 31, lines 27-28).

The Burns et al. invention generally relates to inhalation devices such as metered dose inhalers (MDIs), nebulizers, and dry powder inhalers (col. 1, lines 17-19). MDIs, nebulizers, and dry powder inhalers have been used for many years to treat pulmonary disorders such as asthma (col. 2, lines 28-30). Burns et al. teach that in order for drugs to penetrate deeply into the lung, particles containing the drug should be on the order of a few microns in size (0.2 to 20 μm) (col. 5, lines 38-41). According to Burns et al., aerosol delivery is particularly advantageous because first-pass metabolism of the drug by the liver and kidneys is avoided. In addition, the objectionable requirement of finding a suitable injection site and piercing the skin with a need is avoided. Moreover, according to Burns et al., a wide variety of systemically active drugs would benefit from aerosol delivery via inhalation, including *(inter alia)* antisense, i.e. artificial DNA that causes complementary RNA to self destruct (see col. 5, lines 40-48, and col. 6, lines 61-62).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to design a method for delivering pharmaceutical composition comprising administering to the airways of a subject said pharmaceutical composition in respirable or inhalable particle size of 0.5μm to 10 μm or 10μm to 500μm, comprising at least one antisense oligonucleotide comprising 15% adenosine or less, wherein said antisense oligonucleotide is effective to alleviate asthma. One of ordinary skill in the art would have been motivated to modify the teachings of Krieg et al. with the teachings of Jacobson et al., Debs et al. and Burns et al. to design the invention recited in the instant claims because: 1) Krieg et al. teach that their disclosed immunostimulatory oligonucleotides are capable of being administered to a murine

system and to treat or prevent the symptoms of asthma (see col. 6, lines 59-61); 2) One of ordinary skill in the art would have been motivated to reduce the amount of adenosine present in oligonucleotides used to treat asthma since Jacobson et al. clearly teach that high levels of adenosine results in bronchoconstriction in asthmatics and an exacerbation of the inflammatory and allergic responses. Therefore, in order to reduce the complications associated with high levels of adenosine while treating asthma, the ordinary skilled artisan would have been motivated to use oligonucleotides with reduced adenosine. 3) One of ordinary skill in the art would have been motivated to modify the compounds of Krieg et al. to make formulations or compositions of respirable or inhalable particle size of 0.5μm to 10 μm or 10μm to 500μm, because Debs et al. and Burns et al. clearly teach that particle sizes of a few microns in size (0.2 to 20 μm) can be used to penetrate deeply into the lung for the treatment of asthma.

Therefore, the invention as a whole would have been *prima facie* obvious at the time the invention was made over Krieg et al. in view of Jacobson et al., Debs et al. and Burns et al.

15. Claims 92-106, 108-123 and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schreiber et al. in view of Debs et al. and Burns et al.

Schreiber et al. disclose a method for treating asthma comprising the administration of an antisense construct targeting Syk mRNA (see col. 9, lines 10-22). In one particular embodiment, Schreiber et al. disclose an antisense oligonucleotide targeting Syk mRNA comprising the following sequence: 5'-TGTCTTGTCTTTGTC-3' (see col. 4, lines 44-46). This sequence comprises 0% adenosine and is 15 nucleotides in length. The antisense constructs of Schreiber et al. can be administered systemically or directly to the lung (e.g. aerosol administration).

Delivery can be effected using the techniques described herein (including liposome formulations (see col. 9, lines 17-22).

However, Schreiber et al. does not teach the delivery of pharmaceutical compositions comprising antisense oligonucleotides of a respirable or inhalable particle size of 0.5μm to 10 μm or 10μm to 500μm in size to the airways of a subject.

Debs et al. teach the delivery of nucleic acid compounds to the airways of a patient by means of a nebulizer that produces sufficiently small particles, for example particles of less than 5.0 μm, or more preferably 0.2 to about 4.0 μm. As an alternative to selecting small mean particle diameters to achieve substantial distal airway and alveolar deposition, a very high dosage of the lipid-carrier nucleic acid can be administered with a larger mean particle diameter. A proviso to such an approach is that the particular lipid carrier nucleic acid complex is chosen that is not too irritating at the required dosage and that there be a sufficient diameter in the 0.5 to about 5μm range to allow for deposition in the aveoli. Suitable mean particle diameter will be most preferably from about 5 μm to about 10 μm (see page 31, lines 4-19). Debs et al. teach that nebulizers useful for airway delivery include those typically used in the treatment of asthma (see page 31, lines 27-28).

The Burns et al. invention generally relates to inhalation devices such as metered dose inhalers (MDIs), nebulizers, and dry powder inhalers (col. 1, lines 17-19). MDIs, nebulizers, and dry powder inhalers have been used for many years to treat pulmonary disorders such as asthma (col. 2, lines 28-30). Burns et al. teach that in order for drugs to penetrate deeply into the lung, particles containing the drug should be on the order of a few microns in size (0.2 to 20 μm) (col. 5, lines 38-41). According to Burns et al., aerosol delivery is particularly advantageous because

first-pass metabolism of the drug by the liver and kidneys is avoided. In addition, the objectionable requirement of finding a suitable injection site and piercing the skin with a need is avoided. Moreover, according to Burns et al., a wide variety of systemically active drugs would benefit from aerosol delivery via inhalation, including *(inter alia)* antisense, i.e. artificial DNA that causes complementary RNA to self destruct (see col. 5, lines 40-48, and col. 6, lines 61-62).

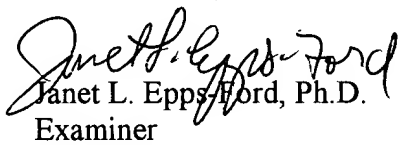
It would have been obvious to one of ordinary skill in the art at the time the invention was made to design a method for delivering pharmaceutical composition comprising administering to the airways of a subject said pharmaceutical composition in respirable or inhalable particle size of 0.5μm to 10 μm or 10μm to 500μm, comprising at least one antisense oligonucleotide comprising 15% adenosine or less, wherein said antisense oligonucleotide is effective to alleviate asthma. One of ordinary skill in the art would have been motivated to modify the teachings of Schreiber et al. with the teachings of Debs et al. and Burns et al. to design the invention recited in the instant claims because: 1) Schreiber et al. teach that their disclosed antisense oligonucleotides targeting Syk mRNA are capable of being used to for treating asthma (see col. 9, lines 10-22; the antisense compound of Schreiber et al. comprising the following sequence: 5'-TGTCTTGTCTTTGTC-3' (see col. 4, lines 44-46) comprises 0% adenosine and is between 7 and 60 nucleotides in length. 2) One of ordinary skill in the art would have been motivated to modify the compounds of Schreiber et al. to make formulations or compositions of respirable or inhalable particle size of 0.5μm to 10 μm or 10μm to 500μm, because Debs et al. and Burns et al. clearly teach that particle sizes of a few microns in size (0.2 to 20 μm) can be used to penetrate deeply into the lung for the treatment of asthma.

Therefore, the invention as a whole would have been *prima facie* obvious over Schreiber et al. in view of Burns et al. and Debs et al.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 571-273-0757.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE